REMARKS

The Official Action dated September 9, 2003 has been carefully considered. Accordingly, the changes presented herewith, taken with the following remarks, are believed sufficient to place the present application in condition for allowance. Reconsideration is respectfully requested.

By the present Amendment, claims 1-3, 6, 8, 11, 13, 18, 22, 23 and 27 are amended for matters of form and clarity. It is believed that these changes do not involve any introduction of new matter, whereby entry is believed to be in order and is respectfully requested.

In the Official Action, claims 1-4 and 6-33 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite. In claim 1, the Examiner questioned the recitation of the zone for addition of liquid containing sample, LZ_n, LZ_m, the meaning of m, and the parenthetical expressions in claims 1, 6, 11, 18, 22 and 27. The Examiner also asserted that claims 6 and 11 were unclear and questioned the definition of m throughout the claims.

However, Applicants submit that claims 1-4 and 6-33 are definite in accordance with the requirements of 35 U.S.C. §112, second paragraph, whereby the rejection has been overcome. Reconsideration is respectfully requested.

More particularly, claim 1 recites that the flow matrix comprises an application zone adapted for application of liquid, which liquid contains buffer and sample and optionally reactants needed for a complete determination, but not Reactant I which is firmly anchored in the matrix (see Section A) in claim 1). Claim 1 further defines the specific liquid application zone for sample as LZ_n-S and the specific liquid application zone for Reactant* as LZ_n-R* (see section c) of claim 1). Further, claim 1 defines m as the total number of application zones in which flow is initiated, whereby LZ_m is the farthest upstream liquid application zone (see

section b) of claim 1). Finally, claim 1 recites that flow is initiated by adding liquid to each liquid application zone LZ in a specified manner. Applicants submit that the definition of liquid application zones in claim 1 and the recitation of application of liquid thereto are clear and consistent in view of the teachings in the present specification.

The present claims also consistently define m, the total number of application zones, as greater than or equal to 2, and the parenthetical expressions objected to by the Examiner have been omitted from the claims. Further, the language in claims 6 and 11 has been clarified in accordance with claim 1 from which they both depend.

It is therefore submitted that claims 1-4 and 6-33 are definite to one of ordinary skill in the art in accordance with the requirements of 35 U.S.C. §112, second paragraph, and that the rejection has been overcome. Reconsideration is respectfully requested.

Claims 1, 3, 7, 9, 10, 13, 14, 18, 20, 21, 24, 25, 27, 28 and 32 were rejected under 35 U.S.C. §102(b) as being anticipated by the Dafforn et al U.S. Patent No. 4,981,786. Claims 2, 4, 6, 8, 11, 19, 22 and 23 were rejected under 35 U.S.C. §103(a) as being unpatentable over Dafforn et al. In response to Applicants' previous arguments, the Examiner asserted that Dafforn et al specifically teach that sample and liquid can be added simultaneously to two different application zones and that the sample is located downstream of the liquid. The Examiner further asserted that one skilled in the art would recognize that if the liquid reagent is added to an application zone and sample is added to a separate application zone simultaneously, that they would both contact the flow matrix almost simultaneously and, since the sample is located downstream of the liquid reagent, the liquid reagent would be transported through the matrix immediately after the sample. The Examiner also asserted that regardless of developer addition as taught by Dafforn et al, the complex will flow towards the detection zone. The Examiner further asserted that if the complex and developer as disclosed

in Daffom are carried together and mixed, the reaction would occur before the detection zone but Daffom et al clearly state that the reaction occurs at the detection zone. The Examiner therefore concludes that the complex binds to the immobilized antibody and then the developer reacts to produce a color change.

However, as set forth in detail below, Applicants submit that the methods, devices and test kit defined by claims 1-4, 6-11, 13, 14, 18-25, 27, 28 and 32 are neither anticipated by nor rendered obvious over Daffom et al. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

More specifically, according to claim 1, the claimed method is for determination of an analyte in a sample in a flow matrix by use of a transport flow of one or more biospecific affinity reactants, at least one of which is analytically detectable (Reactant*) and one of which is firmly anchored in the matrix (Reactant I). The flow matrix comprises A) an application zone adapted for application of liquid (LZ), which liquid contains buffer and sample and optionally reactants needed for a complete determination, but not Reactant I, B) a detection zone (DZ) with the firmly anchored reactant (Reactant I) located downstream of LZ, and C) optionally one or more zones in which any of the reactants needed for a complete determination, but not Reactant I, has been pre-deposited.

The flow towards the detection zone is initiated by addition of the liquid with sample in the application zone LZ for transport of analyte and reactants towards the detection zone (DZ), and the amount of the Reactant* bound to DZ is detected, wherein the detected amount is correlated to the amount of analyte in the sample. The flow matrix comprises at least two application zones for liquid LZ arranged substantially adjacent to each other:

$LZ_m \ldots LZ_n \ldots LZ_l$ DZ

flow direction ⟶ wherein a) LZ_n is an application zone for liquid, and n is the position of the application zone LZ_n, b) m is the total number of application zones in which flow is initiated and is greater than or equal to 2 and is not equal to n, with LZ_m being the farthest upstream liquid application zone, c) one LZ_n is an application zone for sample (LZ_n-S) and one LZ_n is for Reactant* ($LZ_{n''}$-R*) with $n'' \geq n'$; d) ⟶ is the direction of the flow, and e) DZ is the detection zone.

Flow is initiated by adding liquid to each zone LZ_m . . LZ_n . . LZ_1 in such a way that $liquid_{n+1}$, added to the application zone LZ_{n+1}, contacts the flow matrix substantially simultaneously and is transported through the matrix immediately after $liquid_n$ added to the nearest downstream application zone LZ_n.

The device of claim 18 is for determination of an analyte in a sample in a flow matrix by use of a transport flow of one or more biospecific affinity reactants, at least one of which is analytically detectable (Reactant*) and one of which is firmly anchored in the matrix (Reactant I). The device comprises a flow matrix having A) an application zone for liquid (LZ) containing buffer and sample and optionally reactants needed for a complete determination, but not Reactant I, B) a detection zone (DZ) with the firmly anchored reactant (Reactant I) located downstream of LZ, and C) optionally one or more zones in which any of the reactants has been pre-deposited.

The flow matrix comprises at least two application zones for liquid arranged substantially adjacent to each other:

LZ_m . . . LZ_n . . . LZ_1 DZ

⟶

flow direction ⟶ wherein a) LZ_n is an application zone for liquid, and n is the position of the application zone LZ_n, b) m is the total number of application zones

in which flow is initiated and is greater than or equal to 2 and is not equal to n, with LZ_m being the farthest upstream liquid application zone, c) one LZ_n is an application zone for sample ($LZ_{n'}S$) and one LZ_n is for Reactant* ($LZ_{n''}R^*$) with $n'' \geq n'$; d) $\longrightarrow$ is the direction of the flow, and e) DZ is the detection zone.

The device is adapted, when flow is initiated by adding liquid to each zone LZ_m . . LZ_n . . LZ_1 in such a way that $liquid_{n+1}$ added to the application zone LZ_{n+1}, contacts the flow matrix substantially simultaneously to transport the $liquid_{n+1}$ through the matrix immediately after $liquid_n$, added to the nearest downstream application zone LZ_n.

The present methods and devices, allowing substantially simultaneous liquid applications but conducting sequential liquid transport in a manner preserving the order of liquid application zones, facilitate automation of analyte determination, avoid the need for sequential addition of sample and analytically detectable reactant, and allow for predeposited analytical reactant for such methodologies. The presently claimed methods and devices are not taught by Dafforn et al.

Dafforn et al disclose a multiple port assay device. Delivery of a sample may be made into the device through a first means or second means using a dropper, syringe needle, etc., resulting in deposit of the sample on a bibulous strip, and a liquid reagent other than sample may be added to the device. Additional liquid reagents may be added to the device either before or after sample addition, at least one of such reagents being added through the means not used for adding the sample (column 13, lines 32-42). The application of reagents can also be done by breaking an internal liquid-containing container (column 23, line 52).

However, Applicants find no teaching or suggestion by Dafforn et al relating to a method or device as presently claimed wherein at least one biospecific affinity reactant (Reactant I) is firmly anchored in the flow matrix and at least one biospecific affinity reactant

is applied to an application zone in combination with a flow matrix arrangement as recited in claims 1 and 18. Particularly, Applicants find no teaching or suggestion by Dafforn et al of a method or device wherein flow is initiated by adding liquid to each zone in such a way that $liquid_{n+1}$ added to the application zone LZ_{n+1} contacts the flow matrix substantially simultaneously with and is transported through the matrix immediately after $liquid_n$, added to the nearest downstream application zone LZ_n.

In fact, the only specific mention of simultaneous application which Applicants find in the teachings of Dafforn et al is at column 24, beginning at line 22 wherein an assay is described as conducted by adding a sample suspected of containing human chorionic gonadotrophin (HCG) at a first opening and simultaneously adding a developer solution at the second opening. However, contrary to the present methods and device wherein $liquid_{n+1}$ added to the application zone LZ_{n+1} contacts the flow matrix *substantially simultaneously* with and is transported through the matrix *immediately after* $liquid_n$, added to the nearest downstream application zone LZ_n, Dafforn et al disclose that the sample HCG binds to an enzyme conjugate and the resulting complex, namely of HCG and enzyme conjugate, is carried *by the moving developer solution* to the detection zone where it binds, i.e., where the HGC-enzyme conjugate complex binds to the detection zone. Specifically, Dafforn et al disclose:

> The assay can be conducted by adding a sample suspected of containing HCG at the first opening and simultaneously adding a developer solution containing enzyme substrate at the second opening. During subsequent incubation, HCG binds to the conjugate, *the complex carried by the moving developer to the detection zone* where it binds, and the bound complex acts on the substrate to produce color at the detection zone when HCG is present in the sample (column 24, lines 29-37, emphasis added).

Thus, Applicants find no teaching or suggestion by Dafforn et al that liquid reagent contacts a flow matrix *simultaneously* with a sample and is transported through a matrix *immediately*

after the sample. Rather, Dafforn et al teach that HCG-conjugate complex is formed upon addition of sample, and that the thus-formed conjugate is carried *by the moving developer solution* to the detection zone. Dafforn et al provide no teaching or suggestion relating to simultaneous contact with a sequential flow of reagents through a matrix.

Thus, in the present methods and devices, sample and reagent may be applied to the flow matrix simultaneously. The sample begins migration to the detection zone and is followed by liquid migration from the next upstream zone. As a result, there is a continuous migration of sample and reagents through the flow matrix, started by one initial application occasion. The flow of liquids through the flow matrix and the detection zone is in the same order as the liquid application zones. The present methods are advantageous in that sample is provided for reaction in the detection zone, for example with reactant I, prior to contact of sample with the analytically detectable Reactant. Applicants find no such teachings by Dafforn et al.

In the Official Action, page 11, the Examiner asserted that one skilled in the art would recognize that if the liquid reagent is added to an application zone and sample is added to a separate application zone simultaneously, they would both contact the flow matrix almost simultaneously and since the sample is located downstream of the liquid reagent, that the liquid reagent would be transported through the matrix immediately after the sample. The Examiner's assertion regarding the recognition of one skilled in the art is clearly contradictory to the specific teachings of Dafforn et al in that Dafforn et al teach that "*during subsequent incubation, HCG binds to the conjugate, the complex is carried by the moving developer to the detection zone*" (column 24, lines 33-35). Thus, contrary to the Examiner's assertions, Dafforn et al teach that the HCG-enzyme conjugate complex mixes with the developer prior to arrival of the HCG in the detection zone.

The Examiner appears to assert that simultaneous addition of two liquids will inherently result in sequential transport. However, one of ordinary skill in the art will recognize that, as discussed in the present specification, a liquid added in an application zone may have a tendency to spread on top of the matrix to parts of the matrix outside the zone. In fact, Dafforn et al have such mixing as their objective as the developer carries the complex to the detection zone. In contrast, the present methods and devices require sequential transport through the matrix. Moreover, one skilled in the art will also recognize that when a sample introduction port has additional means for sample treatment, for example filtration of a sample, whole blood separation or the like, the delay in flow to the lateral flow matrix from the sample port results in mixture of the sample with a liquid added upstream of the sample addition port. This may well be the explanation for the disclosed mixing of sample-enzyme conjugate complex and developer of Dafforn et al prior to transport of these components to detection zone.

The Examiner also asserted that Dafforn et al clearly state at column 24, lines 35-37 that the reaction occurs at the detection zone. As Dafforn et al clearly state that HCG binds to the enzyme conjugate and the complex is carried by the moving developer to the detection zone, the disclosure at column 24, line 35 of "where it binds, and the bound complex acts on the substrate to produce color at the detection zone" refers to binding of the complex with the immobilized second anti-HCG antibody at the detection zone. There is simply no support for the Examiner's assertion that the complex and developer are not carried together to the detection zone.

With respect to claims 10 and 24, Applicants have argued that Dafforn et al provide no teaching or suggestion of a flow matrix wherein the liquid application zones have zone spacers between each other. The Examiner asserted in the Official Action that the Dafforn et

al device contains dividers or spacers between the first and second means. However, the first and second means of Dafforn et al are provided in the housing 12 merely as wells, and Dafforn et al disclose that the wells 20 and 22 may be designed as a single well with a divider between the two openings. This provides no teaching or suggestion of the elements of claims 10 and 24 wherein the flow matrix comprises liquid application zones having zone spacers therebtween, i.e., in the flow matrix, rather than in a housing well.

Anticipation under 35 U.S.C. §102 requires that each and every element as set forth in the claims is found, either expressly or inherently described, in a single prior art reference, *In re Robertson*, 49 U.S.P.Q.2d 1949, 1950 (Fed Cir. 1999). In view of the deficiencies in the teachings of Dafforn et al with respect to simultaneous contact and sequential transport, Dafforn et al do not anticipate the present claims under 35 U.S.C. §102.

Moreover, Dafforn et al do not render the present methods and devices obvious. That is, in order to render a claimed invention obvious, the prior art must enable one skilled in the art to make and use the claimed invention, *Motorola, Inc. v. Interdigital Tech. Corp.*, 43 U.S.P.Q.2d 1481, 1489 (Fed. Cir. 1997). In view of the failure of Dafforn et al to teach or suggest a method or device employing substantially simultaneous contact of liquids with a flow matrix and sequential flow of the liquids through the flow matrix, Dafforn et al do not enable one of ordinary skill in the art to make and use the claimed invention. In fact, by teaching mixing of the developer with the HCG-enzyme conjugate complex, Dafforn et al teach away from the presently claimed methods and devices. It is error to find obviousness where references diverge from and teach away from the invention at hand, *In re Fine*, 5 U.S.P.Q.2d 1596, 1599 (Fed. Cir. 1988).

Further, the mere fact that prior art could be modified to result in a claimed invention would not have made the modification obvious unless the prior art suggested the desirability

of the modification, *In re Mills*, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). Applicants find no suggestion by Dafforn et al for modifying their teachings along the lines of the presently claimed methods and devices, nor do Applicants find any suggestion by Dafforn et al regarding the desirability of any such modification. Thus, the present methods and devices are nonobvious over Dafforn et al under 35 U.S.C. §103.

It is therefore submitted that the methods and devices defined by claims 1-4, 6-11, 13, 14, 18-25, 27, 28 and 32 are neither anticipated by nor rendered obvious over Dafforn et al, whereby the rejections under 35 U.S.C. §§ 102 and 103 based on Dafforn et al have been overcome. Reconsideration is respectfully requested.

Claims 12, 15, 16, 26, 29 and 30 were rejected under 35 U.S.C. §103(a) as being unpatentable over Dafforn et al in view of the Robinson et al published PCT application WO 95/16914. The Examiner relied on Robinson et al as disclosing the use of calibration zones, and the Examiner asserted it would have been obvious to incorporate the calibrator zone as taught by Robinson et al in to the method and device of Dafforn et al.

However, Applicants submit that the methods and devices defined by claims 12, 15, 16, 26, 29 and 30 are nonobvious over and patentably distinguishable from the combination of Dafforn et al and Robinson et al. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

Claims 12, 15 and 16 depend directly and indirectly, respectively, from claim 1 while claims 26, 29 and 30 depend directly and indirectly, respectively, from claim 18. Claims 12 and 26 recite that at least one reactant other than Reactant* is pre-deposited in an application zone LZ_n-R for liquid intended for transport of the reactant. According to claim 15, the matrix comprises at least one calibrator zone (CZ), in which calibrator is bound to, or in advance has been bound to, the matrix. According to claim 29, the flow matrix comprises at

least one calibrator zone CZ, in which a calibrator or a binder for the calibrator is firmly anchored in the matrix. Claims 16 and 30 recite that the calibrator zone or zones (CZ) of claims 15 and 29, respectively, have a binder for the calibrator firmly anchored in the matrix, the calibrator optionally being pre-deposited in the matrix upstream of the calibrator zone or zones.

The deficiencies of Dafforn et al noted in detail above with respect to claims 1 and 18 apply equally well with respect to claims 12, 15, 16, 26, 29 and 30. Moreover, Appellants find no teaching or suggestion by Dafforn et al relating to an additional zone LZ_n-R as presently claimed, relating to calibration, particularly, integral with their device, or relating to a calibration zone in their device, calibrator predeposited in or applied to a matrix, or a binder for a calibrator in a calibration zone.

These deficiencies of Dafforn et al are not resolved by Robinson et al. Robinson et al describe a sensor device for a sandwich assay comprising a discrete zone having a measurement region on which is immobilized a first specific binding partner for a ligand under assay and a known amount of a releasable optionally labeled second specific binding partner for the ligand under assay, and a second discrete zone having a region on which is immobilized a first specific binding partner for the ligand under assay, a releasable known amount of ligand analog, and a second known amount of a second optionally labeled second specific binding partner for the ligand under assay.

However, Appellants find no teaching or suggestion by Robinson et al of a method or device as recited in claims 1 and 18, respectively, employing at least one analytically detectable biospecific affinity reactant (Reactant*) and at least one firmly anchored biospecific affinity reactant (Reactant I) in a detection zone, with the arrangement of liquid application zones and liquid flows as recited in claims 1 and 18. Additionally, Appellants

find no teaching or suggestion for employing any of the elements of Robinson et al's sensor device in the multiple port assay device of Dafforn et al. In fact, while Dafforn et al require application of one or more liquid reagents in addition to a liquid sample through different introduction means, the sensor device of Robinson et al is designed for a sandwich assay wherein only a sample containing a ligand under assay is applied.

Applicants are not claiming the use of additional reactants calibrator per se. Rather, Applicants are claiming defined methods and devices, in which the flow matrix comprises an additional liquid application zone LZ_n-R (claims 12 and 26) or comprises at least one calibrator zone (CZ), in which calibrator is bound to, or in advance has been bound to, the matrix (claim 15) or in which a calibrator or a binder for the calibrator is firmly anchored in the matrix (claim 29), and optionally which have a binder for the calibrator firmly anchored in the matrix, the calibrator optionally being pre-deposited in the matrix upstream of the calibrator zone or zones (claims 16 and 30). Applicants find no teaching or suggestion for modifying the teachings of Dafforn et al to include any portion of the Robinson et al teachings, and particularly those which would relate to additional liquid application zones or calibration zones, calibrator and binder as recited in the present claims, to arrive at the invention defined by any of claims 12, 15, 16, 26, 29 or 30.

In order to render a claimed invention obvious, the prior art must enable one skilled in the art to make and use the claimed invention, *Motorola, Inc. v. Interdigital Tech. Corp.*, *supra*. In view of the failure of Robinson et al to resolve the deficiencies of Dafforn et al, particularly with respect to a method and device allowing simultaneous application and sequential transport, or to provide any suggestion for combining and modifying the teachings of Robinson et al and Dafforn et al along the lines asserted by the Examiner, the combination of these references simply does not enable one of ordinary skill in the art to conduct the

claimed methods or make and use the claimed devices. Thus, the combination of Dafforn et al and Robinson et al does not render the present claims obvious. It is therefore submitted that the methods and devices defined by claims 12, 15, 16, 26, 29 and 30 are nonobvious over and patentably distinguishable from Dafforn et al and Robinson et al, whereby the rejection under 35 U.S.C. §103 has been overcome. Reconsideration is respectfully requested.

Finally, claims 17 and 31 were rejected under 35 U.S.C. §103(a) as being unpatentable over Dafforn et al in view of the Self U.S. Patent No. 4,446,231. The Examiner relied on Self as disclosing that immunoassays are used for the detection and/or determination of autoimmune diseases. The Examiner concluded it would have been obvious to use the device and method of Dafforn et al for diagnosing autoimmune disease.

However, Applicants submit that the method and device defined by claims 17 and 31 are nonobvious over and patentably distinguishable from the combination of Dafforn et al in view of Self. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

Claim 17 depends directly from claim 1 while claim 31 depends directly from claim 18. These claims recite respectively that the method is performed as part of diagnosing allergy or autoimmune disease and that the device is intended for diagnosing allergy or autoimmune disease.

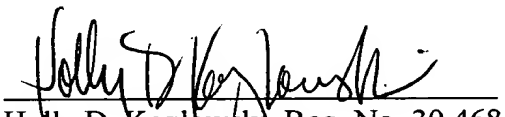
The deficiencies of Dafforn et al noted in detail above with respect to claims 1 and 18 apply equally well with respect to claims 17 and 31. Moreover, Applicants find no specific teaching or suggestion by Dafforn et al relating diagnosing allergy or autoimmune disease.

The deficiencies of Dafforn et al are not resolved by Self. That is, while Self discloses an immunoassay using an amplified cyclic detection system, Applicants find no teaching or suggestion by Self relating to a method or device for determination of an analyte in a sample

and a flow matrix employing a combination of biospecific affinity reactants and liquid application zones and flow as defined in claims 1 and 18. Similarly, Applicants find no teaching or suggestion by Self for modifying any of the teachings of Daffom et al to result in either a method or a device as presently claimed. Thus, the mere teaching by Self of the use of immunoassays for detection and/or determination of autoimmune diseases does not resolve the deficiencies of Daffom et al, particularly with respect to a method and device allowing simultaneous liquid application and sequential liquid transport. Thus, the combination of Daffom et al and Self does not render the methods and devices of the present claims obvious, and the rejection under 35 U.S.C. §103 has been overcome. Reconsideration is respectfully requested.

It is believed that the above represents a complete response to the rejections under 35 U.S.C. §§ 102, 103 and 112, second paragraph, and places the present application in condition for allowance. Reconsideration and an early allowance are requested.

Respectfully submitted,



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